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10/826,729	04/16/2004	Thomas Tibbitts	PTZ-059	1372

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EXAMINER	
ODELL, LINDSAY T	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 04/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/826,729	TIBBITTS, THOMAS	
	Examiner	Art Unit	
	Lindsay Odell	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Claims 1-10 are pending in this instant Office action.

Priority

2. The instant application is granted the benefit of priority for the U.S. provisional Application No. 60/463,810 filed on April 17, 2003 as requested in the declaration and the first lines of the specification.

Compliance with Sequence Rules

3. The sequence listing, filed in computer readable form (CRF) and paper copy on September 10, 2004 has been received and entered.

Objections to the Specification

4. The abstract of the disclosure is objected for not completely describing the disclosed subject matter (MPEP § 608.01(b)). It is noted that in many databases and in foreign countries the Abstract is crucial in defining the disclosed subject matter; thus, its completeness is essential. The Examiner suggests inclusion of the following information, for completeness: 1) Inclusion of the full name for MSPCIT, modulators specific for pin-1 that covalently interact with a target site, given on page 4 of the specification, because the acronym MSPCIT does not clearly describe the invention. 2) Inclusion of the source species of the Pin-1 protein, *Homo sapiens*, as disclosed in the sequence listing, and recitation of the activity of the Pin-1 protein, to catalyze the

isomerization of only phosphorylated Ser/Thr-Pro bonds (disclosed on page 2). 3) Inclusion of the identity of the amino acid residue (i.e. cyteine-113 or serine-114, see pages 3-4) that forms specific covalent interactions with novel compounds. 4) Inclusion of the compounds juglone and Fredericamycin-A as compounds that are able to modulate Pin1 activity by forming a specific covalent interaction with an amino acid residue in the active site of Pin1.

5. The specification is objected to for the improper use of trademarks. The use of the trademarks "TAXOTERE", "PROSCAR", "EULEXIN", "GEMZAR", "ZOLADEX", "KYTRIL", "CAMPTO", "CAMPTOSAR", "ZOFRAN", "TAXOL", "ONCASPAR", "SALAGEN", "PHOTOFRIN", "PROLEUKIN", "RITUXAN", "HYCAMTIN", "HERCEPTIN", "RETIN-A", "TRIAPINE", and "NAVELBINE" have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. Please see page 15 of the specification for instances of improper trademark use. Correction is required.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

6. The disclosure is objected to because of the following informalities: there are blanks in the specification on page 1, line 7 and page 31, line 20 for the US Application entitled "*PHOTOCHEMOTHERAPEUTIC COMPOUNDS FOR USE IN TREATMENT OF PIN1-ASSOCIATED STATES*". Appropriate correction is required.

Claims Objections

7. Claim 9 is objected to because of the following informalities: there is a typo in the phrase "of the **Pin1** active site" (emphasis added). The Examiner suggests changing the word "Pin1", highlighted in bold to ---Pin-1---. Appropriate correction is required.

8. Claim 10 is objected to because of the following informalities: there are two typos in the phrase "with one **of** more of the following areas of the active site" (emphasis added). Examiner suggests changing the "of" highlighted in bold to ---or---, and deleting the extra spaces between the word "of" and the phrase "the active site". Appropriate correction is required.

9. Examiner notes that the claim language used in claim 8 limits the scope of the claim such that further interaction of the instant compounds is to only one of the regions of the Pin-1 polypeptide listed. Interaction with more than one of the regions, as suggested on page 3, lines 28-29 of the specification, is excluded by the claim language. Is this Applicant's intention? If not, Examiner suggests using the language --- further interacts with one or more of the regions--- in place of the language "further interacts with one of the regions".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word "Pin-1" is unclear as to the metes and bounds it imparts on the claimed subject matter. The polypeptide Pin-1 is not so well known in the art that it could not be confused with the acronym for another molecule/disease/organism. The Examiner suggests that Applicant use the following language, which incorporates a clearer identification of Pin-1, found on page 2 of the specification, in the first claim in which Pin-1 appears: --- 1. . . . the peptidyl-prolyl cis-trans isomerase, Pin-1---.

11. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "Pin-1 associated disorder" is unclear as to the metes and bounds it imparts on the claimed subject matter. Examples of what is included by using the term "Pin-1 associated disorder" are disclosed on page 5 of the specification, i.e. abnormal cell growth. However, an explicit definition for the term "Pin-1 associated disorder" is not disclosed in the specification, nor is it clearly defined in the art with a single meaning. It is not clear whether the term "Pin-1 associated disorder", as used in the claims, refers to a disorder caused by Pin-1 malfunction, or if it is any disorder wherein overexpression of Pin-1 is detected. In either case, it is not clear how to evaluate whether or not any particular disorder is a Pin-1 disorder. Clarification is required.

12. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "effective amount" is unclear as to the metes and bounds it imparts on the claimed subject matter. A clear definition for the term "effective amount" is not disclosed in the specification, nor is it clearly defined in the art with a single meaning. On pages 16-17, the specification discloses:

"The language 'effective amount' of the compound is that amount necessary or sufficient to treat or prevent a Pin1 associated state, or a PRTP associated state, e.g. prevent the various morphological and somatic symptoms of a Pin1 associated state".

This definition for the term "effective amount' is confusing because Pin1 associated state or disorder is not explicitly defined, as described above. The amount of a MSPCIT that constitutes an "effective amount" cannot be assessed based on the alleviation of symptoms of an undefined state. Clarification is required.

13. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The abbreviation MSPCIT must be defined upon its first appearance in the claims for clarity. Clarification is required. The Examiner suggests that Applicant use the following language, which incorporates the definition of MSPCIT found on page 4 of the specification, in the first claim in which MSPCIT appears: --- 1. . . . modulator specific for pin-1 that covalently interact with a target site (MSPCIT)---.

14. Claims 2-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitation in claims 2-6 "wherein said MSPCIT . . ." is unclear as to the metes and bounds it imparts on the claimed subject matter. Does the phrase "wherein said MSPCIT . . ." further limit the functional capability of the compound used in the method of treatment? Or does the phrase "wherein said MSPCIT . . ." require that the MSPCIT perform that function in the method of treatment? Clarification is required.

15. Claims 4 and 7-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The reference to residue serine-114 of Pin-1 of the Pin-1 polypeptide is confusing because it is not disclosed in the specification. Does Applicant mean to refer to residue serine-154 as disclosed on page 8, paragraph 1 of the specification? Clarification is required.

16. Claims 4-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The reference to residues cysteine-113 or serine-154 of Pin-1 of the Pin-1 polypeptide is confusing because it is human Pin-1 that has cysteine-113 and serine-154; the analogous residues in other Pin-1 proteins may have different numbering. Does Applicant mean cysteine-113 or serine-154 of human Pin-1 (SEQ ID NO: 1)? Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 1-10 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to a) methods of treating a Pin-1 associated disorder by administering a modulator specific for pin-1 that covalently interact with a target site MSPCIT (claim 1), which optionally interactions with a serine residue (claims 2 and 4) or a cysteine residue (claims 5-6), b) compounds that specifically modulate Pin-1 activity through covalent interaction with cysteine-113 or serine-154 of Pin-1 (claims 7-8), and c) compounds that are capable of a specific covalent interaction with the Pin-1 active site (claims 9-10). Claims 1-10 each contain the functional limitation that the instant modulators or compounds covalently interact with Pin-1. However, adequate description of the structure of all the modulators or compounds claimed as products or used in the claimed methods included in the scope of the claims is lacking.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and

Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (see *Enzo Biochemical*, 63 USPQ2D 1609, CAFC 2002).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both *Lily* and *Enzo Biochemical* to methods of using products, wherein said products lack adequate written description. While in *University of Rochester v. G.D. Searle & Co.* the methods were held to lack written description because not a single example of the product used in the claimed methods was described, the same analysis applies wherein the product, used in the claimed methods, must have adequate written description as noted from Enzo Biochemical (see above).

On pages 36-37, the specification discloses two compounds, juglone and Fredericamycin-A, whose structures are well-known in the art, that covalently interact with *Homo sapiens* Pin-1. Prior art reveals that juglone covalently interacts with cysteine-113 by forming a Michael adduct (Hennig *et al.*, page 5959, see PTO-892). The particular residue that Fredericamycin-A interacts has not been determined. These two species of MSPCIT's, or compounds that covalently interact with the Pin-1 polypeptide, are adequately described. Thus, one species of the genera of

MSPCITs that covalently interacts with a cysteine or with cysteine-113, optionally forming a Michael adduct (juglone), is adequately described; however, no species of the genera of MSPCIT's that covalently interact with a serine or with serine-154 are disclosed, nor are any species of the genus of MSPCIT's that form a disulfide bond with cysteine-113 disclosed.

A sufficient number of MSPCIT's that covalently interact with a serine or cysteine residue, more specifically cysteine-113 or serine-154 of human Pin-1, and a description of the common structural characteristics that define the instant genera of MSPCIT's is lacking. In view of the prior art, one of skill in the art would be unable to predict the structure of members of this genus by virtue of the instant disclosure. Therefore, claims drawn to the instant genera of methods of treating a Pin-1 associated disorder by administering a MSPCIT (claims 1-6) and to compounds that specifically modulate the activity of Pin-1 by covalently interacting with Pin-1 (claims 7-8) or that solely covalently interact with Pin-1 (claims 9-10) are not adequately described.

18. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because, while the art enables methods of treating a Pin-1 associated disorder with juglone and Fredericamycin-A, the specification does not reasonably provide enablement for the genus of methods of treating a Pin-1 associated disorder with any MSPCIT (claim 1) that specifically modulates the activity of Pin-1 by covalently interacting with certain residues of Pin-1 (claims 2-6). The claim(s) contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected,

to make and/or use the invention. To practice the methods encompassed by the scope of the instant claims would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Two working examples of using MSPCIT's in a method to treat a Pin-1 associated disorder are found in the art (see Ping *et al.* and Kapadia *et al.,* PTO-892); the MSPCIT's used in these methods are juglone, which specifically interacts with cysteine-113, and Fredericamycin A. The specification contains no working examples of MSPCIT's or MSPCIT's that interact with particular residues that are used in a method to treat a Pin-1 associated disorder. While the

specification discloses the MSPCIT's juglone and Fredericamycin A, no working examples of using these MSPCIT's or any other MSPCIT's in a method to treat a Pin-1 associated disorder are present. The nature of the invention is such that what constitutes a Pin-1 associated disorder is unclear (see 112, 2nd paragraph rejection), and the MSPCIT's can be any kind of molecule (i.e. protein, peptide, small molecule). While the instant specification describes a methods for finding and identifying MSPCIT's on pages 26-32 of the specification, these methods do not enable one of skill in the art to make all, or a relevant portion of, the MSPCIT's within the scope of the claims. The ability to find a MSPCIT within the scope of the instant claims is not equivalent to the ability to make a MSPCIT required by the statute (i.e., "make and use"). With no guidance as to the features that define a Pin-1 associated disorder or to the common structure of MSPCIT's, the predictability of functionality becomes extremely low. The breadth of the claims and the unpredictability of the art render the instant claims not enabled without undue experimentation.

19. Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for juglone and Fredericamycin-A, does not reasonably provide enablement for the genus of compounds that specifically modulate the activity of Pin-1 by covalently interacting with certain residues of Pin-1 (claims 7-8), or the genus of compounds that are capable of a specific covalent interaction with an amino acid residue of the Pin-1 active site (claims 9-10). To make all the compounds included in the scope of these claims would require undue experimentation. The factors to be considered in determining whether undue experimentation is required are summarized above.

The specification contains two working examples of compounds that covalently interact with Pin-1 and that modulate Pin-1 activity: juglone and Fredericamycin-A, disclosed on pages 36-37 of the specification. Juglone is disclosed in the art as covalently interacting with cysteine-113 (Hennig *et al.,* see PTO-892); however it is unclear what residues Fredericamycin-A covalently interacts with. Thus, no working examples of compounds that specifically interact with serine-154 are present. Few additional working examples are found in the prior art. While the instant specification describes methods for finding and identifying compounds that covalently interact with Pin-1 on pages 26-32 of the specification, these methods do not enable one of skill in the art to make all, or a relevant portion of, the molecules within the scope of the claims. The ability to find a compound that covalently modifies Pin-1 within the scope of the instant claims is not equivalent to the ability to make a compound required by the statute (i.e., "make and use"). The nature of the invention is such that the instant compounds can be any kind of molecule (i.e. protein, peptide, small molecule); and with no guidance in the specification or the art as to the common structure of such molecules, the predictability of functionality becomes extremely low. The breadth of the claims and the unpredictability of the art render the instant claims not enabled to the full extent of their scope without undue experimentation.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

20. Claims 1-10 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. The claims are drawn to methods of treating Pin-1 associated disorders by

administering a MSPCIT to a subject (claims 1-6), to compounds that specifically modulate the activity of Pin-1 by covalently interacting with it (claims 7-8), and to compounds that are capable of covalently interacting with Pin-1 (claims 9-10). To fulfill the utility requirement of 35 U.S.C. 101, an invention must have a specific, substantial, and credible utility that is disclosed in the specification or that is well established as considered by one of ordinary skill in the art. The specification does not teach one specific, substantial and credible utility for modulators or compounds that covalently interact with Pin-1, nor is there a utility well-established in the art. On pages 2-3, the specification discloses that inhibition of Pin1 kills human and yeast dividing cells, and that Pin1 would be a novel target for diseases characterized by uncontrolled cell proliferation, primarily malignancies. However, a specific disease is not named, nor is Pin-1 associated disorder clearly defined (see 112, 2nd paragraph rejection). In addition, the MSPCIT's and compounds included in the scope of the instant claims are not limited to inhibitors, but could be activators (claims 1-10), or could have no effect on Pin-1 activity at all (claims 9-10). Compounds that do not affect Pin-1 activity have no known utility. In addition, without understanding what constitutes a Pin-1 associated disorder and without knowing the affect of activating Pin-1, the utility of a MSPCIT or a compound that covalently interacts with Pin-1 is unclear.

21. Claims 7-10 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. Claims 7-10 are drawn to compounds that covalently interact with Pin-1. The instant claims, as written, do not sufficiently distinguish over compounds as they naturally exist because the claims do not particularly point out any non-naturally occurring

differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. The claim should be amended to indicate the hand of the inventor, e.g. by insertion of "isolated" if support can be found in the specification. See Diamond v. Chakrabarty, 447 U.S. 303, 206, USPQ 193 (1980).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

22. Claims 1 and 9 are rejected under 35 U.S.C. § 102(e) as being anticipated by Ping *et al.* (see PTO-892) as evidenced by Tibbitts (PGPUBs NO: 20050004024, see PTO-892). The instant claims are drawn to a method of treating a Pin-1 associated disorder in a subject by administering a MSPCIT (claim 1) and a compound that is capable of covalent interaction with an amino acid residue of the Pin1 active site (claim 9).

Ping *et al.* teach treating a Pin 1-associated state by administering Fredericamycin A. Fredericamycin A constitutes an MSPCIT because it modifies the activity of Pin-1 (see Figure 3)

and specifically covalently modifies the Pin-1 active site as disclosed by Tibbitts (see page 13, column 2). Thus, the teachings of Ping *et al.* anticipate claims 1 and 9.

23. Claims 1, 3 and 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kapadia *et al.* (see PTO-892), as evidenced by Hennig *et al.* (see PTO-892). The instant claims are drawn to methods of treating Pin-1 associated disorders comprising administering a MSPCIT to a subject (claim 1), the MSPCIT optionally covalently interacting with a cysteine (claims 3), that cysteine being optionally being cysteine-113 (7-8).

Kapadia *et al.* teach that the administration of juglone to mice has an inhibitory effect on mouse skin carcinogenesis (see pages 48-50, test compound 13 and page 52, Figure 3). Kapadia *et al.* anticipate claims 1, 3 and 5 for two reasons. First, in the broadest reasonable interpretation of the claims, skin carcinogenesis can be considered a "Pin-1 associated disorder" because it is a type of abnormal cell growth (see 112, 2nd paragraph rejection). Second, juglone is a MSPCIT, as shown by Hennig *et al.* who teach that juglone inactivates human Pin-1 (see page 5956, Figure 1) and covalently modifies human Pin-1 residue cysteine-113 (see page 5959, column 2, paragraph 4). This covalent interaction is as the result of a Michael-type addition, making it a Michael-adduct (see Hennig *et al.*, page 5957-5958), which meets the requirement for claim 5. Thus, the teachings of Kapadia have anticipated claims 1, 3 and 5 because they have taught a MSPCIT that forms a Michael adduct with cysteine-113 of human Pin-1, which they administer in a method to treat a Pin-1 associated disorder.

24. Claim 7 is rejected under 35 U.S.C. § 102(b) as being anticipated by Hennig *et al.* (see PTO-892). The instant claim is drawn to compounds that modulate the activity of Pin-1 and covalently interact with cysteine-113 (claim 7).

Hennig *et al.* teach that juglone, inactivates human Pin-1 (see page 5956, Figure 1), and that it covalently modifies human Pin-1 residue cysteine-113 (see page 5959, column 2, paragraph 4). The teachings of Hennig *et al.*, thus, anticipate claim 7.

25. Claim 9 is rejected under 35 U.S.C. § 102(b) as being anticipated by Hennig *et al.* (see PTO-892) as evidenced by Ranganathan *et al.* (see PTO-892). The instant claim is drawn to compounds that are capable of covalent interaction with an amino acid residue of the Pin-1 active site (claim 9).

Hennig *et al.* teach that juglone modifies human Pin-1 residue cysteine-113 (see page 5959, column 2, paragraph 4), as described above. Residue cysteine-113 is disclosed as being a human Pin-1 active-site residue by Ranganathan *et al.* (see pages 890-891). The teachings of Hennig *et al.*, thus, anticipate claim 9 because they have taught a compound that inherently covalently interacts with cysteine-113, an active site residue.

26. Claims 8 and 10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hennig *et al.* (see PTO-892) as evidenced by Tibbitts (PGPUBs NO: 20050004024, see PTO-892). The instant claims are drawn to compounds that modulate the activity of Pin-1, covalently interact with cysteine-113 of Pin-1 and interact with a particular region of the Pin-1 polypeptide (claim

8), and to compounds that are capable of covalent interaction with an amino acid residue of the Pin-1 active site and interact with a particular region of the active site of Pin-1 (claim 10).

Hennig *et al.* teach that juglone inactivates human Pin-1 (see page 5956, Figure 1), and that it covalently modifies human Pin-1 residue cysteine-113 (see page 5959, column 2, paragraph 4), as described above. Residue cysteine-113 is disclosed as being part of "the substrate entry groove" by Tibbitts (see page 3, column 2), which is designated as part of the active site of Pin-1 in claim 10. The teachings of Hennig *et al.*, thus, anticipate every aspect of claims 8 and 10 because they have taught a compound that inherently specifically modulates the activity of Pin-1 by covalently interacting with cysteine-113, an active site residue, and additionally interacting with the "substrate entry groove".

Conclusion

27. Claims 1-10 are rejected for the reasons identified in the numbered sections of the Office action. Applicants must respond to the objections/rejections in each of the numbered sections in the Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lindsay Odell whose telephone number is 571-272-3445. The examiner can normally be reached on M-F, 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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March 30, 2005

KATHLEEN KERR, PH.D.
PRIMARY EXAMINER